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Synthesis and SAR of highly potent dual 5-HT$_{1A}$ and 5-HT$_{1B}$ antagonists as potential antidepressant drugs

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Abstract—Novel 5-HT$_1$ autoreceptor ligands based on the *N*-4-aryl-piperazinyl-*N*′-ethyl-5,6,7,8-tetrahydropyrido[4′, 3′:4,5]thieno[2,3-d]pyrimidin-4(3*H*)-one core are described. Aiming at antidepressants with a novel mode of action our objective was to identify potent antagonists showing balanced affinities and high selectivity for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors. Strategies for the development of dual 5-HT$_{1A}$ and 5-HT$_{1B}$ antagonists based on **1** and **2** as leads and the corresponding results are discussed. Isoquinoline analogue **33** displayed high affinity and an antagonistic mode of action for the 5-HT$_{1A}$ and the 5-HT$_{1B}$ receptors and was characterized further with respect to selectivity, electrically stimulated [^{3}H]5-HT release and in vivo efficacy.

Major depression is a mental disorder characterized by persistent periods of a set of symptoms such as depressed mood, irritability, low self-esteem, feelings of hopelessness and worthlessness, loss of interest in activities or pleasurable stimuli, decreased energy, and recurrent thoughts of death and suicide.[1] The disease is associated with considerable impairment in a patient's quality of life, functional disability, and loss of productivity, and poses a major public and economic health problem.[2–4]

Although a number of new hypotheses have emerged during the last years, the pathophysiological mechanisms underlying depression remain poorly understood.[5] Numerous clinically effective antidepressants act via increasing extracellular serotonin (5-HT) levels either by blocking 5-HT reuptake or degradation, thus supporting the hypothesis that enhancement of 5-HT neurotransmission might underlie the therapeutic response to these different antidepressants.[6,7] Today selective serotonin reuptake inhibitors (SSRIs) have emerged as first-line antidepressant therapy due to their improved side-effect profile.[8] However, a major limitation of the current SSRIs is their slow onset of action of up to six weeks, and their lack of efficacy in more than 30% of the depressed patients.[9] Hence, there is a large medical need for the development of novel antidepressants with improved efficacy, faster onset of action, and better tolerability.

Amongst the various 5-HT receptors, the 5-HT autoreceptors, in particular, have received considerable attention as potential targets for antidepressant action.[10] 5-HT efflux in the dorsal raphe nucleus is regulated by the 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1D}$ receptor subtypes, each differentially located and with slightly different, possibly even parallel, roles.[11–13] Comparing the pharmacological properties across species, only the rodent 5-HT$_{1B}$ subtype stands out. Rat and human 5-HT$_{1B}$ receptor (the latter previously termed as 5-HT$_{1D\beta}$) show a single amino acid modification and were found to have different pharmacology, whereas the pharmacological profile for both the 5-HT$_{1A}$ and the 5-HT$_{1D}$ subtypes was shown to be well conserved among different species.

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In contrast, and despite their relatively low homology, the human 5-HT_{1D} and 5-HT_{1B} subtypes are pharmacologically remarkably similar and thus are virtually indistinguishable in native tissue.[14]

For several years 5-HT_{1A} agonists have been evaluated for antidepressant efficacy, but despite the fact that 5-HT_{1A} agonists like buspirone have been shown to exert anxiolytic and antidepressant effects in humans, results from clinical trials have been disappointing so far.[15] In contrast, 5-HT_{1A} antagonists were recently shown to exert anxiolytic-like effects.[16] Additional data suggest that co-administration of a 5-HT_{1A} antagonist accelerates and potentiates the antidepressant efficacy of SSRIs. However, first trials were proving to be inconsistent.[17,18] Blockade of 5-$HT_{1B/D}$ autoreceptors has been proposed as an alternative approach towards novel antidepressants.[19] Recently, the efficacy of AR-A2, a selective 5-$HT_{1B/D}$ antagonist, has been demonstrated in behavioral models of depression, and the compound is reported to be in phase II clinical trials.[20]

It has been suggested that 5-HT autoreceptor activation at least contributes to the limitations of SSRI efficacy in two ways: reduction in 5-HT neuronal firing due to an activation of somatodendritic 5-HT_{1A} autoreceptors by locally released 5-HT, and second, a reduction of 5-HT release in terminal areas resulting from increased 5-HT in the synapse activating 5-$HT_{1B/D}$ receptors. Chronic antidepressant treatment will then lead to autoreceptor desensitization, and the time required for desensitization relates to the delayed onset of action observed in antidepressant therapy.

Hence, we envisaged that a strategy for circumventing these adverse autoinhibitory effects could be to block the 5-HT autoreceptors simultaneously, which should lead to a rapid and massive increase in 5-HT levels, and is expected to result in a faster onset of action and improved antidepressant efficacy. This hypothesis was supported by in vivo microdialysis studies showing that concurrent blockade of the 5-HT_{1A} and 5-$HT_{1B/D}$ receptor subtypes resulted in a significant and synergistic increase of extracellular 5-HT in guinea pig frontal cortex.[21] However, to date, SB-272183 is the only 5-$HT_{1A/B/D}$ antagonist described in the literature, but neither in vivo data nor any further development has been reported (Fig. 1).[22]

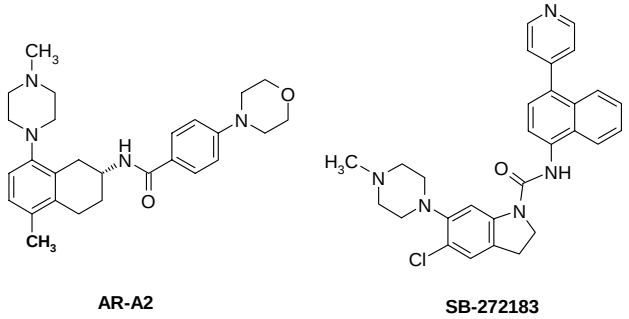


Figure 1.

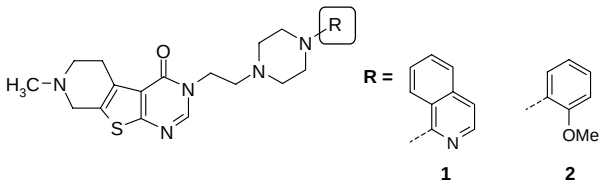


Figure 2. Lead structures **1** and **2**.

Herein, we describe the synthesis and characterization of new 5-HT_{1A} and 5-HT_{1B} ligands based on the *N*-aryl-piperazinyl-*N*′-ethyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-4(3*H*)-one core. We also present SAR derived from modification in the aryl part with respect to affinity, selectivity, and functional properties. Selected compounds were examined for selectivity against a set of related cloned human receptors, in vitro 5-HT release, PK properties, and in vivo efficacy in a behavioral model of depression.

Sequence alignment and molecular modeling[23] indicated only minor differences in the ligand binding site of 5-HT_{1B} and 5-HT_{1A} receptors. Thus, our goal of achieving combined antagonists seemed to be feasible. The tetrahydropyridothienopyrimidinones **1** and **2** were chosen as attractive leads since they already offered high affinity and the required balanced binding profile for the 5-HT_1 autoreceptors, whereas functional antagonism remained the primary goal for further optimization (Fig. 2).

Careful analysis of available SAR data led to the hypothesis that the functional properties within this series are determined by the nature of the *N*-aryl-piperazine moiety. This hypothesis was supported by modeling suggesting that the orientation of Asp95 on TM2[24] determines the functional properties of both the 5-HT_{1A} and the 5-HT_{1B} receptors.[25,26] Modeling revealed an interaction between the isoquinolinyl-nitrogen in **1** and Asp95, aligning the carboxyl group in the 'agonist orientation' (Fig. 3A); a similar model could be assembled for the corresponding 2-methoxyphenyl analogue **2**. We hypothesized that disruption of this interaction via modification in the aryl part of the molecule would alter Asp95 to an 'antagonist' orientation. Hence, we focused our efforts on modification of the 'right-hand side' aromatic moiety since the tetrahydropyridothienopyrimidinone core and the C2 linker had been found to be optimal with respect to 5-HT_1 affinity in previous studies.

Early on in this project α_1 cross-activity had been identified as potential issue in our lead series, since inhibition of α adrenergic receptors is known to interfere with the cardiovascular system and thus might lead to side effects.[27] Previous results in this series indicated that α_1 affinity could be affected by modification in the tetrahydropyridothienopyrimidinone core, either by exchange of the N-methyl group or by variation adjacent to the pyrimidinone carbonyl, thus impeding the interaction between carbonyl group and the receptor. We decided, however, to focus first on achieving the desired dual antagonism for both the 5-HT_{1A} and 5-HT_{1B} receptors

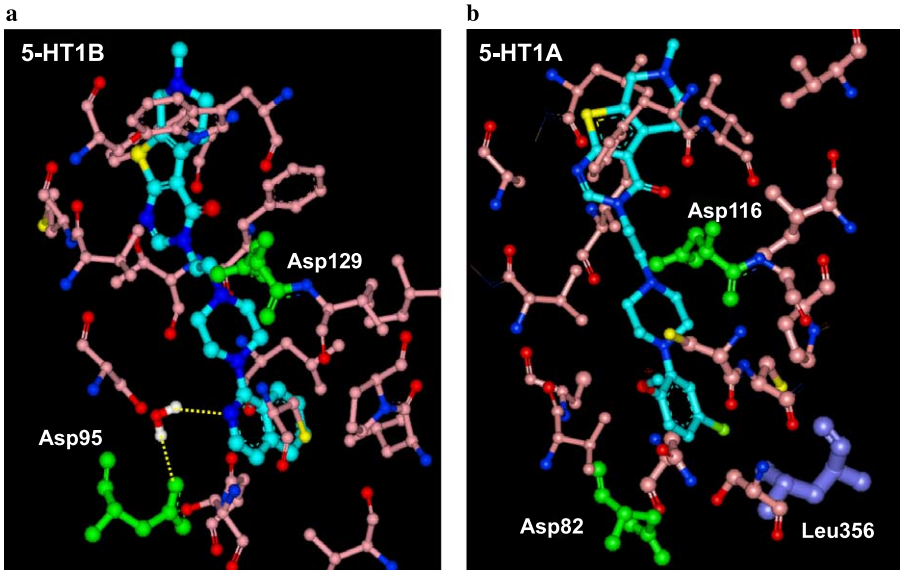
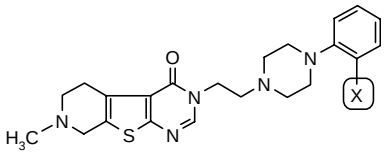


Figure 3. (a) Modeling structure of compound **1** in the 5-HT_{1B} receptor. Shown are the amino acid residues assembling the ligand binding site. In green: Asp95 and Asp129, the latter binding to the piperazine N (numbering of amino acids cf. Ref. 24). (b) Structure of compound **21** in the 5-HT_{1A} receptor. Leu 356 (see text) is indicated in purple.

as the more challenging, and in terms of proof of concept, the more important task, and to address α_1 selectivity subsequently. Nevertheless, affinity data for α_1 have been determined routinely for all analogues and are included in Tables 1–4.

Scheme 1 depicts the general synthesis of *N*-aryl-piperazinyl-*N*′-ethyl-5,6,7,8-tetrahydropyrido[4′, 3′:4,5]thieno[2,3-d]pyrimidin-4(3*H*)-one based derivatives.[28] Condensation of 4-methylpiperidine-4-one with ethyl cyanoacetate and sulfur according to a procedure originally described by Gewald,[29] assembly of the annelated 3-substituted pyrimidinone and conversion into the chloride afforded key intermediate **5**, which was further reacted with the respective piperazine derivatives to give final products **1**, **2**, and **13**–**41**. The various (het)aryl piperazines applied in the synthesis were prepared following one of the routes as exemplified in Scheme 2 for intermediates **8** and **12**. Nucleophilic amination according to Buchwald-Hartwig[30] using *tert*-butyl piperazine-1-carboxylate (quinoline-, isoquinoline-piperazines, and benzothien-7-ylpiperazine, cf. Scheme 1) with subsequent deprotection, or assembly of the piperazine starting from the corresponding aniline precursor using bis(chloroethyl)amine (various substituted aryl piperazines, 2,3-dihydro-1-benzofuran-7-ylpiperazine[31]), gave the desired piperazine derivatives. The required starting materials were either commercially available or prepared according to generally known procedures.[32]

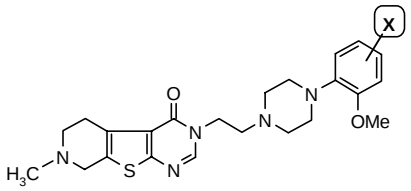
Table 1. Variation of aryl substituent in position 2



Compounds	X	K_i (nM)[a]/function[b]		α_1 K_i (nM)[a]
		5-HT_{1A}	5-HT_{1B}	
2	OMe	**0.7/AN**	**1.4/pA**	**0.4**
13	CH_3	2.9/AN	3.5 / pA	1.7
14	Ph	4.1/pA	1.1/AN	1.1
15	Cl	2.8/pA	1.7/pA	1.0
16	CN	2.5/pA	1.4/A	1.8
17	O^{i}Pr	0.7/pA	2.5/AN	0.1
18		2.5/pA	5.4/AN	0.2
19	OPh	0.9/pA	1.1/pA	0.5
20	OBzl	1.9/pA	1.2/pA	4.0

[a] Values are geometric means of two or three experiments.
[b] AN = antagonist, pA = partial agonist, A = agonist as described.[34]

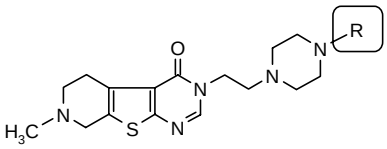
Table 2. Effect of additional substituents in 2-methoxy-arylpiperazine series

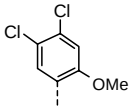
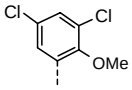
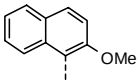


Compounds	X	K_i (nM)[a]/function[b]		α_1 K_i (nM)[a]
		5-HT_{1A}	5-HT_{1B}	
2	H	**0.7/AN**	**1.4/pA**	**0.4**
21	5-Cl	3.0/AN	70.3/AN	0.1
22	5-OMe	24.2/AN	50.2/AN	8.4
23	5-CH_3	5.6/pA	11.9/AN	12.1
24	5-CF_3	103.9/nd	42.3/nd	18.0
25	5-Ph	429.0/nd	116.4/nd	0.1
26	4-Cl	18.8/pA	3.3/AN	0.5
27	3-Cl	2.5/pA	0.5/pA	7.0

[a] Values are geometric means of two or three experiments.
[b] AN = antagonist, pA = partial agonist, A = agonist as described.[34]

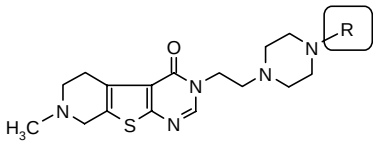
Table 3. SAR of poly-substitued or bicyclic (het)aryl substituents

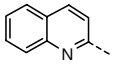


Compounds	R	K_i (nM)[a]/function[b]		α_1 K_i (nM)[a]
		5-HT_{1A}	5-HT_{1B}	
28		2.5/pA	4.9/AN	0.2
29		25.8/A	3.8/pA	14.8
30		11.8/pA	5.4/pA	4.5
31		0.6/pA	0.5/AN	0.2
32		0.4/pA	0.4/AN	0.5

[a] Values are geometric means of two or three experiments.
[b] AN = antagonist, pA = partial agonist, A = agonist as described.[34]

Table 4. SAR within the quinoline and isoquinoline series



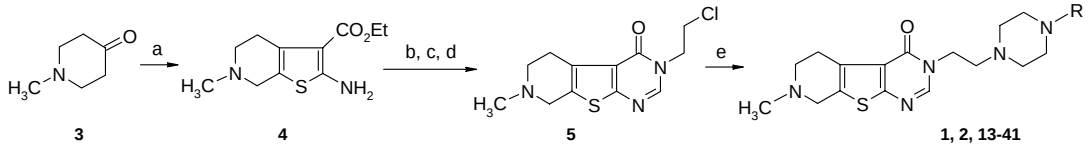
Compounds	R	K_i (nM)[a]/function[b]		α_1 K_i (nM)[a]
		5-HT_{1A}	5-HT_{1B}	
1		**0.7/pA**	**0.5/pA**	**41.1**
33		4.7/AN	2.5/AN	13.7
34		6.5/AN	9.7/AN	118.1
35		1.5/AN	1.7/pA	26.7
36		0.9/pA	0.9/pA	129.1
37		0.3/pA	0.1/pA	1.2
38		0.2/pA	0.3/pA	1.2
39		93.4/AN	319.6/A	6780
40		9.1/pA	36.6/pA	121.1
41		0.7/pA	0.5/pA	13.2

[a] Values are geometric means of two or three experiments.
[b] AN = antagonist, pA = partial agonist, A = agonist as described.[34]

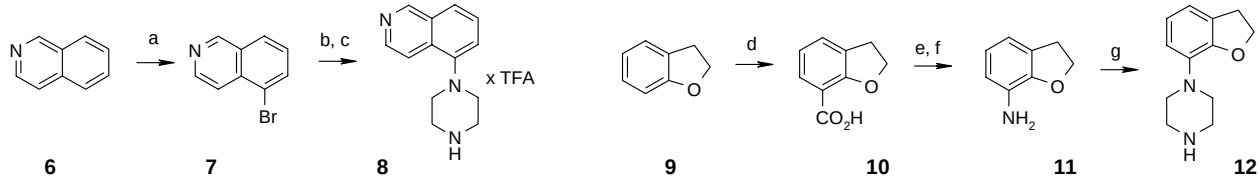
Final compounds **1**, **2**, and **13**–**41** were evaluated for receptor affinity via radioligand binding assays using human recombinant 5-HT_{1A}, 5-HT_{1B}, and α_1 receptors.[33] Furthermore, affinity for the human recombinant 5-HT_{1D} receptor was determined routinely. As expected, affinity for 5-HT_{1D} was found to parallel 5-HT_{1B} affinity, hence for reasons of clarity these data have not been included in the SAR tables. Functional profiles were determined for compounds displaying K_i values for 5-HT_{1A} and 5-HT_{1B} <100 nM using either [^{35}S]GTPγS binding (5-HT_{1A}) or FLIPR (5-HT_{1B} co-expressed with the G-protein chimera Gqo5 in HEK293 cells). Assignment of functional properties in vitro was calculated as percentage of the maximal response to 5-HT (Emax), and an intrinsic activity qualifier was assigned.[34] The results are depicted in Tables 1–4.

Following our hypothesis of Asp95 interaction as main determinant for intrinsic activity, we started with simple modification of the 2-methoxy group in **2** to explore basic SAR for this substituent (Table 1, compounds **13**–**20**). Whereas methyl analogue **13** retained the affinity and efficacy of **2**, phenyl analogue **14** unexpectedly showed reversed intrinsic activity for the 5-HT_{1A} and 5-HT_{1B} receptors, respectively, an effect which is not understood. Exchange of methoxy with electron-withdrawing substituents (**15**, **16**) resulted in retained affinity but shifted the intrinsic activity for both receptor subtypes to (partial) agonism. Variation of the alkoxy substituent (**17**–**20**) again led to reversed intrinsic activity for 5-HT_{1A} and 5-HT_{1B} in the case of the alkyl analogues (**17**, **18**), whereas the phenoxy and benzyloxy derivatives **19** and **20** were shown to be partial agonists in vitro.

Next, we examined the effect of additional substitution in the aryl moiety of **2** (Table 2). Starting with chlorine as substituent, 2-methoxy-5-chloro analogue **21** displayed the desired antagonist profile. Modeling of **21** suggested that the 5-chlorine atom interferes with Leu356 residue on TM6, shifting the benzene ring of **21** toward TM2 so that there is no room for the interaction of the 2-methoxy group with Asp82 via a water molecule (Fig. 3b). As a consequence, the Asp82 side-chain conformation is changed, and compound **21** is an antagonist at both the 5-HT_{1A} and 5-HT_{1B} receptors. However, the achievement of dual antagonism was associated with a 50-fold reduction in affinity versus 5-HT_{1B}. A similar trend, although more pronounced in the case



Scheme 1. Reagents and conditions: (a) S_8, ethyl cyanoacetate, morpholine, EtOH/60 °C (89%); (b) triethyl orthoformiate, acetic acid anhydride/reflux; (c) aminoethanol, EtOH/reflux; (d) $SOCl_2$, dichloroethane/rt (61% from **4**); (e) *N*-arylpiperazine, NaBr, DIEA, NMP/110 °C.



Scheme 2. Reagents and conditions: (a) NBS, H_2SO_4/−20 °C (52%); (b) *tert*-butyl piperazine-1-carboxylate, NaO′Bu, BINAP, $Pd_2(dba)_3$, toluene/80 °C (72%); (c) TFA, CH_2Cl_2 (91%); (d) BuLi, TMEDA, CO_2, *n*-heptane/−70 °C to rt (70%); (e) NaN_3, TFA, TFAA/rt; (f) NaOH, CH_3OH/reflux (58% from **10**); (g) bis(chloroethyl)amine hydrochloride, chlorobenzene/reflux (91%).

of 5-HT_{1A}, was observed with the corresponding 2,5-dimethoxy derivative **22**. K_i values >50 nM for 5-HT_{1B} prevented us from further advancing compounds **21** and **22**. Additional variation in position 5 either led to partial agonism toward the 5-HT_{1A} receptor (**23**) or resulted in a significant loss in affinity for all 5-HT_1 receptor subtypes in parallel (**24**, **25**). Migration of the additional chloro substituent to the 4- or 3-position (**26**, **27**) again enhanced especially 5-HT_{1B} affinity, with 2-methoxy-3-chloro analogue **26** showing the most balanced affinity in this series. To exploit the beneficial effect observed for 5-chloro substitution in **21**, analogues featuring increased bulk in the aryl moiety were prepared (Table 3). The corresponding bis-chloro analogues **28**, and **29** and naphthyl derivative **30** showed improved 5-HT_{1B} affinity, but none of these compounds retained the initial promising functional profile of **21** or **22**. Constraining the methoxy group of **2** by incorporation into a dihydrofuran ring (**31**) led to high affinities for all three 5-HT_1 receptor subtypes, but also for α_1. Dihydrofuran **31** displayed antagonism for 5-HT_{1B}, but only partial agonism for 5-HT_{1A}. A similar result was obtained with the corresponding thienyl analogue **32**. All analogues from the 'aryl series' (Tables 1–3) were found to show low α_1 selectivity, which was only marginally affected by variation in the aryl moiety.

We then directed our efforts to the related quinoline series as alternative approach (Table 4). Based on **1** as starting point migration of nitrogen around the ring system (entries **33**–**38**) revealed that N in the 3- or 4-position resulted in the desired antagonist profile for 5-HT_{1A} and 5-HT_{1B}. As already observed for analogue **21**, affinity was diminished, in this case by a factor of 5–20. Binding affinity in this series was highest for derivatives **1**, **37**, and **38**, but these analogues did not exhibit the desired functional profile. Combination of the favorable features from **1** and **34** by incorporating N in the 2- and 4-position in quinazoline **39** led to dramatic reduction in affinity. Exchange of the N-location and the piperazine linkage (**40**) resulted in diminished affinity, again especially pronounced in the case of 5-HT_{1B}. The corresponding naphthyl analogue **41** again showed high affinity, but did not display balanced antagonism. Besides the effects already discussed here, we found that most of the compounds from the quinoline/isoquinoline series (Table 4) showed α_1 selectivity higher than those of their corresponding 'aryl' analogues (Tables 1–3).

Summarizing the data presented in Tables 1–4, most analogues derived from aryl variation in **1** and **2** retained the high affinity for the 5-$HT_{1A/B}$ receptors. With respect to intrinsic activity, the SAR we obtained is inconclusive for both the 5-HT_{1A} and 5-HT_{1B} receptors. Whereas the dual antagonist profile of compounds like **22**, **23**, or **33** corroborates our initial working hypothesis, the intrinsic activity observed for compounds such as **30** or **41** does not comply with our functional model. One explanation for this discrepancy could be a different binding mode of these analogues. Nevertheless, these results either reflect the difficulties in predicting the mode of action and/or reveal our incomplete understanding of the correlation between 5-$HT_{1A/B}$ structure and function, respectively.

Based on the results depicted in Table 5 (K_i values 5-$HT_{1A/B}$ <10 nM and an antagonist mode of action for 5-HT_{1A} and 5-HT_{1B}), compounds **33** and **34** were selected for further characterization. Affinity for the corresponding rat receptors was found to be in a comparable range for 5-HT_{1A}, and about a factor of 10 lower for 5-HT_{1B} with K_i values for r5-HT_{1A} of 16.3 nM (**33**) and 23.0 nM (**34**), and for r5-HT_{1B} of 33.1 nM (**33**) and 116.8 nM (**34**). Although displaying limited selectivity versus α_1 adrenoceptors, selectivity of at least 50-fold against related human serotonergic and dopaminergic receptors was observed (Table 6). Moreover, at concentrations of up to 10 μM no inhibition of monoamine transporter function was found (5-HT, dopamine or norepinephrine transporters; results not shown). To further evaluate the effect on 5-HT autoreceptor function, compounds were investigated for their ability to influence electrically stimu-

Table 5. Functional profiles for **33** and **34**

Compounds	[^{35}S]GTPγ S E_{max} (%)	5-HT$_{1A}$IC$_{50}$ (nM)[a]	FLIPR E_{max} (%)	5-HT$_{1B}$ IC$_{50}$ (nM)[a]
33	4	316	7	35
34	6	1304	9	85

[a] Values are geometric means of two or three experiments.

Table 6. Counter screening results for **33** and **34**

Receptor K_i (nM)	**33**	**34**
5-HT$_{2A}$	180	1.200
5-HT$_{2C}$	>10.000	5.500
5-HT$_{5A}$	>10.000	>1.000
5-HT$_7$	520	4.480
D$_3$	1.180	1.300
D$_{2L}$	1.200	1.460
α_1	13.7	118

Values are geometric means of two or three experiments.

lated [^{3}H]5-HT-release from rat brain cortical slices. At concentrations of 0.1 and 1 μM, compound **33** evoked a dose-dependent increase of [^{3}H]5-HT-release confirming the antagonist mode of action. Pharmacokinetic studies of **33** in rat showed metabolic stability and bioavailability after iv- and po-dosing (2 and 10 mg/kg, respectively), and good CNS penetration (10 mg/kg po; *F*: 11 %; brain plasma ratio of 10.2/AUC$_{0-8h}$). Upon in vivo examination in the mouse forced swim test, a behavioral model to assess antidepressant efficacy,[35] compound **33** did not show any significant activity up to 30 mg/kg ip.

Nevertheless, tool compound **33** will be examined in additional behavioral assays and different species to confirm our hypothesis and to further validate the rationale for the synthesis of dual 5-HT$_{1A/B}$ antagonists.

In summary, we have identified novel and potent combined 5-HT$_1$ autoreceptor ligands containing the *N*-4-aryl-piperazinyl-*N*′-ethyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-4(3*H*)-one core. The compounds prepared displayed affinities in the low nanomolar range for human 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1D}$ receptor subtypes. Furthermore, several analogues exhibited an antagonist mode of action for both the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors. In general, the structural modifications we applied had only limited effect on in vitro binding, but major impact on the intrinsic activity for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes. Although we achieved our initial goal, the rational design of balanced 5-HT$_{1A/B}$ antagonists still presents a major challenge since the SAR with respect to the mode of action is not fully understood. Compounds **33** and **34** were chosen as most promising representatives and submitted to further characterization in in vitro and in vivo testing. In counter screening, both compounds showed high selectivity against a set of related receptors with the exception of α_1 adrenoceptors. Although **33** was shown to increase [^{3}H]5-HT release from rat brain cortical slices, an antidepressant-like effect in vivo in the mouse forced swim test could not be demonstrated. Further studies using **33** as tool compound will be conducted to evaluate the potential of dual 5-HT$_{1A/B}$ antagonists.

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References and notes

1. Doris, A.; Ebmeier, K.; Shajahan, P. *Lancet* **1999**, *354*, 1369.
2. Hirschfeld, R. M.; Montgomery, S. A.; Keller, M. B.; Kasper, S.; Schatzberg, A. F.; Moller, H. J.; Healy, D.; Baldwin, D.; Humble, M.; Versiani, M.; Montenegro, R.; Bourgeois, M. *J. Clin. Psychiatry* **2000**, *61*, 268.
3. Holden, C. *Science* **2000**, *288*, 39.
4. Pelissolo, A.; Lepine, J.-P. In *Perspectives in Psychiatry Vol. 8, Epidemiology of Depression and Anxiety Disorder*; Montgomery, S. A., den Boer, J. A., Eds., 2nd ed.; Wiley & Sons: Chichester, UK, 2001.
5. Slattery, D. A.; Hudson, A. L.; Nutt, D. J. *Fundam. Clin. Pharm.* **2004**, *18*, 1.
6. Nestler, E. J.; Barrot, M.; Dileone, R. J.; Eisch, A. J.; Gold, S. J.; Monteggia, L. M. *Neuron* **2002**, *34*, 13.
7. (a) Sun, M. K.; Alkon, D. L. *Curr. Drug Targets* **2002**, *1*, 575; (b) Vetulani, J.; Nalepa, I. *Eur. J. Pharmacol.* **2000**, *405*, 351.
8. (a) Snow, V.; Lascher, S.; Mottur-Pilson, C. *Ann. Intern. Med.* **2000**, *132*, 738; (b) Williams, J. W.; Mulrow, C. D.; Chiquette, E.; Noel, P.; Aguilar, C.; Cornell, J. *Ann. Intern. Med.* **2000**, *132*, 743; (c) Nutt, D. *Eur. Neuropsychopharmacol.* **2000**, *10*(Suppl. 4), S433.
9. (a) Spinks, D.; Spinks, G. *Curr. Med. Chem.* **2002**, *9*, 799; (b) Peretti, S.; Judge, R.; Hindmarch, I. *Acta. Psychiatr. Scand.* **2000**, *403*, 17, Supplementum.
10. (a) Lanfumey, L.; Hamon, M. *Curr. Drug Targets—CNS Neurol. Disord.* **2004**, *3*, 1; (b) Middlemiss, D. N.; Price, G. W.; Watson, J. M. *Curr. Opin. Pharmacol.* **2002**, *2*, 18.
11. Stamford, J. A.; Davidson, C.; McLaughlin, D. P.; Hopwood, S. E. *Trends Neurosci.* **2000**, *23*, 459.
12. (a) Martin-Ruiz, R.; Ugedo, L. *Neuropharmacology* **2001**, *41*, 72; (b) Pullar, I. A.; Boot, J. R.; Broadmore, R. J.; Eyre, T. A.; Cooper, J.; Dsanger, G. J.; Wedley, S.; Mitchell, S. N. *Eur. J. Pharm.* **2004**, *493*, 85; (c) Moret, C.; Briley, M. *Neuropharmacology* **1997**, *36*, 1713.
13. Bidmon, H. J.; Schleicher, A.; Wicke, K.; Gross, G.; Zilles, K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2001**, *363*, 364.
14. Barnes, N. B.; Sharp, T. *Neuropharmacology* **1999**, *38*, 1083.
15. Heiser, J. F.; Wilcox, C. S. *CNS Drugs* **1998**, *10*, 343.

16. (a) Barros, M.; Mello, E. L., Jr.; Maior, R. S.; Müller, c. P.; de Souza Silva, M. A.; Carey, R. J.; Huston, J. P.; Tomaz, C. *Eur. J. Pharm.* **2003**, *482*, 197; (b) Cao, B. J.; Rodgers, R. J. *Neurosci. Biobehav. Rev.* **1998**, *23*, 247.
17. (a) Artigas, F.; Romero, L.; de Montigny, C.; Blier, C. *Trends Neurosci.* **1996**, *19*, 378; (b) Rabiner, E. A.; Gunn, R. N.; Castro, M. E.; Sargent, P. A.; Cowen, P. J.; Koepp, M. J.; Meyer, J. H.; Bench, C. J.; Harrison, P. J.; Pazos, A.; Sharp, T.; Grasby, P. M. *Neuropsychopharmcology* **2000**, *23*, 285.
18. Mewshaw, R. E.; Zhou, D.; Zhou, P.; Shi, X.; Hornby, G.; Spangler, T.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2004**, *47*, 3823.
19. Moret, C.; Briley, M. *Eur. J. Pharmacol.* **2000**, *404*, 1.
20. (a) Ahlgren, C.; Eriksson, A.; Tellefors, P.; Ross, S. B.; Stenfors, C.; Malmberg, A. *Eur. J. Pharmacol.* **2004**, *499*, 67; (b) Stenfors, C.; Hallerbäck, T.; Larsson, G.; Wallsten, C.; Ross, S. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2004**, *369*, 330;(c) AstraZeneca development pipeline: NCEs and line extensions; AstraZeneca plc Company World Wide Web site October 06, 2004.
21. (a) Roberts, C.; Price, G. W.; Jones, B. J. *Eur. J. Pharmacol.* **1997**, *326*, 23; (b) Stenfors, C.; Magnusson, T.; Larsson, L. G.; Yu, H.; Hallbus, M.; Magnusson, O.; Ross, S. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1999**, *359*, 110.
22. (a) Watson, J.; Roberts, C.; Scott, C.; Kendall, I.; Collin, L.; Day, N. C.; Harries, M. H.; Soffin, E.; Davies, C. H.; Randall, A. D.; Heightman, T.; Gaster, L.; Wyman, P.; Parker, C.; Price, G. W.; Middlemiss, D. N. *Br. J. Pharmacol.* **2001**, *133*, 797; (b) Roberts, C.; Price, G. W.; Middlemiss, D. N. *Brain Res. Bull.* **2001**, *56*, 463.
23. Methods and modeling software according to: Hutchins, C. W. *Endocrin. J.* **1994**, *2*, 7.
24. The amino acid numbers mentioned in the text refer to the residues in the h5-HT_{1B} sequence and correspond to the 5-HT_{1A} sequence as follows: Asp95/5-HT_{1B}-Asp82/5-HT_{1A}; Asp129/5-HT_{1B} to Asp116/5-HT_{1A}.
25. (a) Yao, B. B.; Hutchins, C. W.; Carr, T. L.; Cassar, S.; Masters, J. N.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Neuropharmacology* **2003**, *44*, 773; (b) von Geldern, T. W.; Hutchins, C. W.; Kester, J. A.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 957.
26. The model discussed here is in contradiction to a functional model suggested by other authors Gaster, L. M.; Blaney, F. E.; Davies, S.; Duckworth, D. M.; Ham, P.; Jenkins, S.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Mulholland, K. R. *J. Med. Chem.* **1998**, *41*, 1218.
27. Hoffmann, B. B.; Lefkowitz, R. J.. In Gilmann, A. G., Rall, T. W., Nies, A. S., Taylor, P., Eds., 8th ed.; The Pharmacological Basis of Therapeutics; Pergamon Press: New York, USA, 1990.
28. Detailed synthetic protocols in: Steiner, G.; Schellhass, K.; Lubisch, W.; Holzenkamp, U.; Starck, D.; Knopp, M.; Szabo, L.; Emling, F.; Garcia-Ladona, F. X.; Hofmann, H. P.; Unger, L. DE 19900545, 2000; *Chem. Abstr.* **2000**, *133*, 89541.
29. Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333.
30. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
31. Joiner, G. F.; Gaster, L. M. WO 9511243, 1995; *Chem. Abstr*. **1995**, *123*, 198831.
32. Martinez-Esparza, J.; Oficialdegui, A. M.; Perez-Silanes, S.; Begona, H.; Orus, L.; Palop, J. A.; Lasheras, B.; Roca, J.; Mourelle, M.; Bosch, A.; Del-Castillo, J. C.; Tordela, R.; Del Rio, J.; Monge, A. *J. Med. Chem.* **2001**, *44*, 418.
33. Assay setup and screening procedures: Bakker, H. M.; Hornberger, W.; Kling, A.; Lange, U. E. W.; Mack, H.; Moeller, A., Schellhaas, L.; Schmidt, M.; Steiner, G. ; Wicke, K. WO 2004055024, 2004; *Chem. Abstr.* **2004**, *141*, 89095.
34. The intrinsic activity qualifier was assigned according to: A = agonist (GTPγS: $E_{max} > 70\%$; FLIPR: $E_{max} > 80\%$); pA = partial agonist (FLIPR: $20\% < E_{max} < 80\%$; GTPγ S: $10\% < E_{max} < 70\%$); AN = antagonist (GTPγ S: $E_{max} < 10\%$; FLIPR: $E_{max} < 20\%$).
35. Cryan, J. F.; Markou, A.; Lucki, I. *Trends Pharmacol. Sci.* **2002**, *23*, 238.